REMARKS

With entry of this amendment, Claims 27-34 and 43-50 are pending. Claims 27 and 43-50 have been amended. Support for the amendment to Claim 27 can be found on page 34, paragraph 2 of the specification. Support for the amendments to Claims 43-50 can be found on page 7, paragraph 4 and on pages 15 and 17 of the specification. No new matter has been added by these amendments. Claims 35-42 have been cancelled.

Claim Objection

Claims 35-42 have been objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have cancelled these claims rendering the objection moot. The Examiner is requested to withdraw this objection.

35 U.S.C. §103(a)

Claims 27-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Clark *et al.* (hereinafter Clark), in view of Patel *et al.* (hereinafter Patel). Claims 35-42 have been cancelled, thereby rendering moot their rejection. The Office Action states that "one of ordinary skill in the art would be motivated to use the method of [Patel] to clone the baculovirus of Clark for the expected benefit of reducing time consumption and reducing cost due to the lack of need for rounds of plaque purification and the ability to isolate multiple recombinants simultaneously. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods of [Patel] *et al.* by the addition of yeast selectable markers to the baculovirus of Clark *et al.* such that a baculovirus vector that can replicate in yeast is produced. Applicants traverse this rejection.

Applicants assert that Clark discloses a recombinant baculovirus expression system that is not capable of being maintained in an intermediate host. In order to replicate the virus using the system described by Clark, a host cell such as *T. ni* must be used. Additionally, unlike the present invention, the system disclosed in Clark can still replicate at low levels in normal insect cells. The system disclosed by Clark therefore produces baculovirus with mutation as well as baculovirus vectors containing foreign gene inserts contaminated by parental baculovirus without those inserts. It requires considerable work to remove contaminating parental viral particles and renders the stock of virus unusable for repeat experimentation or as a control. (*See* Fraser, M.J. et al., Acquisition of Host Cell DNA Sequences by Baculoviruses: Relationship between Host DNA Insertions and FP Mutants *Autographa califonica* and *Galleria mellonella* Nuclear Polyhedrosis Viruses. (1995) Virology 47, 287-300, attached.)

Patel requires the introduction of a transfer vector with the foreign gene into a yeast cell containing the fully infectious baculovirus genome. The baculovirus DNA must then be recovered from each yeast strain containing the recombinant virus and purified on a sucrose gradient to ensure infectivity. (Patel, page 99, left hand column, paragraph 2) In contrast, in the claimed invention, a stock of defective baculovirus DNA, purified once from bacteria, is combined with various transfer vectors to make recombinant viruses in insect cells. The system of the present invention is therefore suitable for high throughput production of recombinant viruses in a manner not permitted by the system of Patel.

Furthermore, there is no teaching, motivation or suggestion to combine Clark with Patel. Even if Patel and Clark were combined, they would not suggest, teach or disclose the present invention. The combination of Patel and Clark would result in a system that uses the yeast cell for recombination, not the insect cell as currently claimed, and which would require an extra purifying step to remove the virus DNA from the yeast cells for each recombinant virus made. Accordingly, the present

invention is not disclosed, taught or suggested by Clark in view of Patel. Applicants respectfully assert that the rejection under 35 U.S.C. §103(a) has been overcome and request its withdrawal.

35 U.S.C. §103(a)

Claims 27-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kitts *et al.,* (hereinafter Kitts) in view of Patel. Claims 35-42 have been cancelled, thereby rendering moot their rejection. The Office Action states that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kitts "that teaches cloning of a foreign gene by restoring replication function to a replication defective baculoviral genome with the teachings of Patel *et al.* concerning replication and maintenance of the baculoviral genome in yeast because Kitts teaches that it is within the skill of the art to use replication defective baculovirus for cloning foreign genes and Patel *et al.* teach that it is within the skill of the art to grow baculovirus in yeast." Applicants traverse this rejection.

The system taught in Kitts requires that the virus DNA be digested prior to use. This will always leave some DNA intact as an infectious circular molecule that can initiate infection in insect cells and will produce background virus without a foreign gene. Accordingly, unlike the above-referenced application, the method of Kitts requires multiple screening steps to remove contaminant parental virus.

Patel is simply directed towards producing a recombinant baculovirus. The infectious recombinant virus is made in the yeast cell, which is then recovered as DNA and introduced into the insect cells. In the present invention as claimed, the insertion of foreign DNA is not carried out in the yeast cell as taught by Patel, but in an insect cell. The use of the insect cell host allows the production of replication-deficient virus in high concentrations that are easily purified. No restriction enzyme digestion is required to produce the replication deficiency and the method produces

sufficient replication deficiency to obviate the need for plaque assays to further purify the virus and remove any residual parental virus.

The yeast system of Patel requires the introduction of a transfer vector with the foreign gene into the yeast cell containing the fully infectious baculovirus genome. Recombination and selection of the yeast colonies ensures that the foreign gene is inserted into the virus genome. However, the baculovirus DNA must be recovered from each yeast strain containing the recombinant virus. Further, Patel recommends that the DNA be purified on a sucrose gradient to ensure infectivity. (Patel, page 99, left hand column, paragraph 2) In contrast, in the claimed invention, a stock of defective baculovirus DNA, purified once from bacteria, is combined with various transfer vectors to make recombinant viruses in insect cells. The system of the present invention is therefore suitable for high throughput production of recombinant viruses in a manner not permitted, suggested or taught by the system of Patel.

There is no teaching, motivation or suggestion to combine Kitts with Patel. Even if they were combined, they would result in system that recombined in the yeast cells and not in an insect cell as currently claimed and would require additional purification steps, thereby preventing high throughput production. For at least the reasons stated above, Applicants respectfully assert that the rejection under 35 U.S.C. §103(a) has been overcome and request its withdrawal.

35 U.S.C. §103(a)

Claims 27-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Blissard *et al.* (U.S. Patent No. 5,750,383) in view of Patel. Claims 35-42 have been cancelled, thereby rendering moot their rejection. The Office Action asserts that "it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Blissard *et al.* that teaches rescue of a replication defective baculoviral genome through transfer of a foreign gene with the replication

defective gene with the teachings of Patel *et al.* concerning replication and maintenance of the baculoviral genome in yeast because Blissard *et al.* teach that it is within the skill of the art to use replication defective baculovirus for cloning foreign genes and Patel *et al.* teach that it is within the skill of the art to grow baculovirus in yeast." Applicants traverse this rejection.

The system used by Blissard uses whole virus particles which infect the cell at a different time than the foreign DNA resulting in a heterogeneous population. The reason is because when virus particles enter the insect cells, even though they are defective because of their lack of GP64, they eventually replicate after recombination as recombinant virus is made. This results in a portion of the population lacking the foreign gene insert. In contrast, in the present invention, the naked DNA of the baculovirus is used. The use of the naked DNA allows the transfection of cells with the baculovirus vector and the foreign DNA simultaneously resulting in a homogenous population.

The aim of Patel is to use the yeast cell instead of insect cells, to produce recombinant viruses. Applicants' invention results in the efficient production of vectors comprising foreign DNA without requiring restriction enzyme digestion to produce the replication deficiency thereby obviating the need for plaque assays to further purify the virus and remove any residual parental virus. This means that the claimed invention can be used for high throughput assays using the single step of applying the naked baculovirus to the cell at the same time as the foreign DNA. Additionally, the system disclosed by Patel uses yeast that is not replication deficient to modify baculoviruses. In contrast, the present invention does not use the yeast cell to modify the baculovirus, but simply uses the yeast to allow the baculovirus vector to be replicated.

The use of the yeast system of Patel requires the introduction of a transfer vector with the foreign gene into the yeast cell containing the fully infectious baculovirus genome. Recombination and selection of the yeast colonies ensures that

the foreign gene is inserted into the virus genome. However, the baculovirus DNA must be recovered from each yeast strain containing the recombinant virus. Further, Patel recommends that the DNA be purified on a sucrose gradient to ensure infectivity. (Patel, page 99, left hand column, paragraph 2) In contrast, in the claimed invention, a stock of defective baculovirus DNA, purified once from bacteria, is combined with various transfer vectors to make recombinant viruses in insect cells. The system of the present invention is suitable for high throughput production of recombinant viruses in a manner not permitted, suggested or taught by the system of Patel.

There is no teaching, motivation or suggestion to combine Blissard with Patel. Even if they were combined, they would result in system that recombined in the yeast cells and not in an insect cell as currently claimed would require additional purification steps thereby preventing high throughput production. Applicants respectfully assert that the rejection under 35 U.S.C. §103(a) has been overcome and request its withdrawal.

35 U.S.C. § 112

Claims 31-34 and 39-42 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 39-42 have been cancelled, thereby rendering moot their rejection. "Given the large size and diversity of the Baculovirus family (hundreds of different viruses), the diversity of the recited genes, the absence of disclosed or art recognized correlations between structure and function and the large number of potential fragments and mutations, it must be considered that any functional fragment or mutation must be empirically determined." Applicants traverse this rejection.

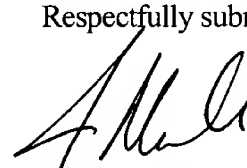
Applicants respectfully assert that the identification of functional fragments or mutations is a matter of routine experimentation, not undue experimentation. Titles such as Kool (1995) "Replication of Baculovirus DNA", Lu (1995) "The role of eighteen baculovirus late expression factor genes in transcription and DNA replications", and Lu (1997) "Baculovirus DNA replication" must be considered to reflect the state of mind of an artisan of ordinary skill in the art. A person skilled in the art, if using a baculovirus that is not exemplified, would be able to identify functional genes in that baculovirus by following the same methods used to identify the functional genes in known baculoviruses. Once the functional gene is identified, a person skilled in the art would be able to readily identify functional fragments or mutations without undue experimentation. The separate genes recited in the claims indicate functional genes that are common within baculoviruses and have been well characterized in the art. For example, *dna pol* is ubiquitous, and would not be difficult to find, identify, fragment or mutate while still preserving a functional gene. Several other genes including *lef-2, lef-8* and *ie-1* are also found universally in baculoviruses.

The assay for functionality is a simple one in that replication is either enabled or not enabled in the baculovirus. The prior art presented in the information disclosure statement is full of assays to determine whether a baculovirus is capable of replicating or not when a gene is removed, fragmented or mutated. Indeed, page 31 paragraph 3 of the application provides one of many alternative ways of identifying the critical parts of any particular protein (*lef-2* in this case). Hence, one such way of identifying a target for deletion or mutation is given in the application. The identification of functional fragments does not involve undue experimentation. It is standard, routine work. Accordingly, the claims of the present invention are described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully assert that the rejection under 35

U.S.C. §112, second paragraph, has been overcome and request its withdrawal.

Applicants respectfully submit that this is a complete response to the Office Action dated July 1, 2003 and that Claims 27-34 and 43-50 are patentable. Early and favorable consideration is earnestly solicited. If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,



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